BLINCYTO- blinatumomab
Amgen Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BLINCYTO™ safely and effectively. See full prescribing information for BLINCYTO.

BLINCYTO (blinatumomab) for injection, for intravenous use
Initial U.S. Approval: 2014

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3), (5.1)**
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3), (5.2)**

INDICATIONS AND USAGE

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials. (1)

DOSAGE AND ADMINISTRATION

- Dosage
  - Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. (2)
  - A single cycle of treatment consists of 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval. (2.1)
  - For patients at least 45 kg in weight, in Cycle 1, administer BLINCYTO at 9 mcg/day on Days 1–7 and at 28 mcg/day on Days 8–28. For subsequent cycles, administer BLINCYTO at 28 mcg/day on Days 1–28. (2.1)
- Administration
  - Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 day 8), or when restarting an infusion after an interruption of 4 or more hours. (2.2)
  - Administer as a continuous intravenous infusion at a constant flow rate using an infusion pump. (2.2)
  - The IV bag should be infused over 24 hours or 48 hours. (2.2)
  - BLINCYTO should be infused through a dedicated lumen. (2.2)
- Preparation
  - IV Solution Stabilizer is provided and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO. (2.4)
  - Reconstitute BLINCYTO with Sterile Water for Injection, USP, only. (2.4)
  - Aseptic technique must be strictly observed when preparing the solution for infusion since BLINCYTO does not contain antimicrobial preservatives. (2.4)
  - Use the specific volumes described in the admixing instructions. (2.4)

DOSAGE FORMS AND STRENGTHS

- For injection: 35 mcg of lyophilized powder in a single-use vial for reconstitution. (3)

CONTRAINDICATIONS

- Known hypersensitivity to blinatumomab or to any component of the product formulation. (4)

WARNINGS AND PRECAUTIONS

- Infections: Monitor patients for signs or symptoms and treat appropriately. (5.3)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. (5.6)
- Preparation and Administration Errors: Strictly follow instructions for preparation (including admixing) and administration. (5.9)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 20%) were pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

There is limited experience in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. *[See Dosage and Administration (2.3), Warnings and Precautions (5.1)].***
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. *[See Dosage and Administration (2.3), Warnings and Precautions (5.2)].***

1. INDICATIONS AND USAGE

BLINCYTO is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials *[see Clinical Studies (14.1)]*.

2. DOSAGE AND ADMINISTRATION

Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

Do not flush the BLINCYTO infusion line especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. Preparation and administration errors resulting in overdose have occurred *[see Dosage and Administration (2.2 and 2.4) and Warnings and Precautions (5.9)]*.

2.1 Dosage

- A single cycle of treatment of BLINCYTO consists of 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval.
- For patients at least 45 kg in weight:
  - In Cycle 1, administer BLINCYTO at 9 mcg/day on Days 1–7 and at 28 mcg/day on Days 8–28.
  - For subsequent cycles, administer BLINCYTO at 28 mcg/day on Days 1–28.
- Allow for at least 2 weeks treatment-free between cycles of BLINCYTO.
- A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation treatment (up to a total of 5 cycles).

2.2 Administration

- Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 day 8), or when restarting an infusion after an interruption of 4 or more hours.
- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- BLINCYTO infusion bags should be infused over 24 hours or 48 hours *[see Dosage and Administration (2.4)]*. Infuse the total 240 mL BLINCYTO solution according to the instructions on the pharmacy label on the bag at one of the following constant infusion rates:
  - Infusion rate of 10 mL/h for a duration of 24 hours, OR
  - Infusion rate of 5 mL/h for a duration of 48 hours
- The BLINCYTO solution for infusion must be administered using IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.
- **Important Note: Do not flush the infusion line, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage. BLINCYTO should be infused through a dedicated lumen.**
- At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV lines should be disposed of in accordance with local requirements.

2.3 Dosage Adjustments

If the interruption after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.

Toxicity	Grade*	Action
Cytokine Release Syndrome (CRS)	Grade 3 -	Withhold BLINCYTO until resolved, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue

		- BLINCYTO permanently.
Neurological Toxicity	Seizure	Discontinue - BLINCYTO permanently if more than one seizure occurs.
	Grade 3	Withhold - BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Discontinue - BLINCYTO permanently.
Other Clinically Relevant Adverse Reactions	Grade 3	Withhold - BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Consider - discontinuing BLINCYTO

permanently.

* Based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening.

2.4 Reconstitution and Preparation of Solution for Infusion

It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose) *[see Warnings and Precautions (5.9)]*.

Call 1-800-77-AMGEN (1-800-772-6436) if you have questions about the reconstitution and preparation of BLINCYTO.

2.4.1 Gather Supplies

NOTE: 1 package BLINCYTO includes 1 vial of BLINCYTO and 1 vial of IV Solution Stabilizer.

Before preparation, ensure you have the following supplies ready:

- 1 package of BLINCYTO for preparation of 9 mcg/day dose infused over 24 hours at a rate of 10 mL/h, 9 mcg/day dose infused over 48 hours at a rate of 5 mL/h, and 28 mcg/day dose infused over 24 hours at a rate of 10 mL/h
- 2 packages of BLINCYTO for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/h

The following supplies are also required, but **not** included in the package:

- Sterile, single-use disposable syringes
- 21- to 23- gauge needle(s) (recommended)
- Preservative-free Sterile Water for Injection, USP
- 250 mL 0.9% Sodium Chloride IV bag
  - To minimize the number of aseptic transfers, it is recommended to use a 250 mL-prefilled IV bag. 250 mL-prefilled IV bags typically contain overfill with a total volume of 265 to 275 mL. **BLINCYTO dose calculations provided in section 2.4.4 are based on a starting volume of 265 mL to 275 mL 0.9% Sodium Chloride.**
  - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA IV tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter
  - Ensure that the IV tubing is compatible with the infusion pump.

2.4.2 Aseptic Preparation

Aseptic technique must be strictly observed when preparing the solution for infusion since BLINCYTO vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare BLINCYTO according to aseptic standards, including but not limited to:

- Preparation must be done in a USP <797> compliant facility.
- Preparation must be done in an ISO Class 5 laminar flow hood or better.
- The admixing area should have appropriate environmental specifications, confirmed by periodic monitoring.
- Personnel should be appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Personnel should wear appropriate protective clothing and gloves.
- Gloves and surfaces should be disinfected.

2.4.3 SPECIAL CONSIDERATIONS TO SUPPORT ACCURATE PREPARATION

A) IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to IV bags and IV lines. **Therefore, add IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride. Do not use IV Solution Stabilizer for reconstitution of BLINCYTO.**

B) The entire volume of the admixed BLINCYTO will be more than the volume administered to the patient (240 mL) to account for the priming of the IV line and to ensure that the patient will receive the full dose of BLINCYTO.

C) When preparing an IV bag, remove air from IV bag. This is particularly important for use with an ambulatory infusion pump.

D) Use the specific volumes described in the admixing instructions *[see Dosage and Administration*

(2.4.4)] to minimize errors in calculation.

2.4.4 Preparation of BLINCYTO Solution for Infusion Using a Prefilled 250 mL 0.9% Sodium Chloride IV Bag

Specific admixing instructions are provided for each dose and infusion time. Verify the prescribed dose and infusion time of BLINCYTO and identify the appropriate dosing preparation section listed below. Follow the steps for reconstituting BLINCYTO and preparing the IV bag.

- See section 2.4.4.1 for 9 mcg/day infused over 24 hours at a rate of 10 mL/h.
- See section 2.4.4.2 for 9 mcg/day infused over 48 hours at a rate of 5 mL/h.
- See section 2.4.4.3 for 28 mcg/day infused over 24 hours at a rate of 10 mL/h.
- See section 2.4.4.4 for 28 mcg/day infused over 48 hours at a rate of 5 mL/h.

2.4.4.1 Preparation of BLINCYTO 9 mcg/day infused over 24 hours at a rate of 10 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.5 mL of **IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride**. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vial.
3. Using a 5 mL syringe, reconstitute one vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
   - The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 1 mL syringe, aseptically transfer 0.83 mL of reconstituted BLINCYTO into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and **prime the IV line only with the prepared solution for infusion**. **Do not prime with 0.9% Sodium Chloride.**
8. Store at 2°C to 8°C if not used immediately.

2.4.4.2 Preparation of BLINCYTO 9 mcg/day infused over 48 hours at a rate of 5 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.5 mL of **IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride**. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vial.
3. Using a 5 mL syringe, reconstitute one vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
   - The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 1.7 mL of reconstituted BLINCYTO into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and **prime the IV line only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride.**
8. Store at 2°C to 8°C if not used immediately.

2.4.4.3 Preparation of BLINCYTO 28 mcg/day infused over 24 hours at a rate of 10 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of **IV Solution Stabilizer to the IV bag with**

0.9% Sodium Chloride. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vial.

3. Using a 5 mL syringe, reconstitute one vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
   - The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 2.6 mL of reconstituted BLINCYTO into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and **prime the IV line only with the prepared solution for infusion**. **Do not prime with 0.9% Sodium Chloride.**
8. Store at 2°C to 8°C if not used immediately.

2.4.4.4 Preparation of BLINCYTO 28 mcg/day infused over 48 hours at a rate of 5 mL/h

1. Use a prefilled 250 mL 0.9% Sodium Chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% Sodium Chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of **IV Solution Stabilizer to the IV bag with 0.9% Sodium Chloride**. Gently mix the contents of the bag to avoid foaming. Discard remaining IV Solution Stabilizer vials.
3. Use two vials of BLINCYTO. Using a 5 mL syringe, reconstitute each vial of BLINCYTO using 3 mL of preservative-free Sterile Water for Injection, USP. Direct preservative-free Sterile Water for Injection, USP, toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
   - The addition of preservative-free Sterile Water for Injection, USP, to the lyophilized powder results in a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colorless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 5.2 mL of reconstituted BLINCYTO into the IV bag (2.7 mL from one vial and the remaining 2.5 mL from the second vial). Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and **prime the IV line only with the prepared solution for infusion**. **Do not prime with 0.9% Sodium Chloride.**
8. Store at 2°C to 8°C if not used immediately.

2.5 Storage Requirements

The information in Table 1 indicates the storage time for the reconstituted BLINCYTO vial and prepared IV bag containing BLINCYTO solution for infusion. Lyophilized BLINCYTO vial and IV Solution Stabilizer may be stored for a maximum of 8 hours at room temperature.

Table 1. Storage Time for Reconstituted BLINCYTO and IV Solution Stabilizer

Maximum Storage Time of Reconstituted BLINCYTO Vial*		**Maximum Storage Time of Prepared IV Bag Containing BLINCYTO Solution for Infusion**	
Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
4 hours	24 hours	48 hours†	8 days

* While stored, protect BLINCYTO and IV Solution Stabilizer vials from light.

† Storage time includes infusion time. If IV bag containing BLINCYTO solution for infusion is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

3. DOSAGE FORMS AND STRENGTHS

For injection: 35 mcg of lyophilized powder in a single-use vial for reconstitution.

4. CONTRAINDICATIONS

BLINCYTO is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation.

5. WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.

Infusion reactions have occurred with the BLINCYTO infusion and may be clinically indistinguishable from manifestations of CRS.

Serious adverse events that may be associated with CRS included pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin; these events infrequently led to BLINCYTO discontinuation. Life-threatening or fatal CRS was infrequently reported in patients receiving BLINCYTO. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

Patients should be closely monitored for signs or symptoms of these events. Management of these events may require either temporary interruption or discontinuation of BLINCYTO *[see Dosage and Administration (2.3)]*.

5.2 Neurological Toxicities

In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 50% of patients. The median time to onset of any neurological toxicity was 7 days. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities, and interrupt or discontinue BLINCYTO as recommended *[see Dosage and Administration (2.3)]*.

5.3 Infections

In patients receiving BLINCYTO in clinical trials, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25% of patients, some of which were life-threatening or fatal. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used for the prevention of TLS during BLINCYTO treatment. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of BLINCYTO *[see Dosage and Administration (2.3)]*.

5.5 Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO. Monitor laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO infusion. Interrupt BLINCYTO if prolonged neutropenia occurs.

5.6 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including seizures, patients receiving BLINCYTO are at risk for loss of consciousness *[see Warnings and Precautions (5.2)]*. Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered.

5.7 Elevated Liver Enzymes

Treatment with BLINCYTO was associated with transient elevations in liver enzymes. Although the majority of these events were observed in the setting of CRS, some were observed outside of this

setting. For these events, the median time to onset was 15 days. In patients receiving BLINCYTO in clinical trials, Grade 3 or greater elevations in liver enzymes occurred in approximately 6% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment. Interrupt BLINCYTO if the transaminases rise to greater than 5 times the upper limit of normal or if bilirubin rises to more than 3 times the upper limit of normal.

5.8 Leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and antileukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

5.9 Preparation and Administration Errors

Preparation and administration errors have occurred with BLINCYTO treatment. Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including underdose and overdose) *[see Dosage and Administration (2.2) and (2.4)]*.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurological Toxicities *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Neutropenia and Febrile Neutropenia *[see Warnings and Precautions (5.5)]*
- Effects on Ability to Drive and Use Machines *[see Warnings and Precautions (5.6)]*
- Elevated Liver Enzymes *[see Warnings and Precautions (5.7)]*
- Leukoencephalopathy *[see Warnings and Precautions (5.8)]*
- Preparation and Administration Errors *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to BLINCYTO in clinical trials in which 212 patients with relapsed or refractory ALL received up to 28 mcg/day. All patients received at least one dose of BLINCYTO. The median age of the study population was 37 years (range: 18 to 79 years), 63% were male, 79% were White, 3% were Asian, and 3% were Black or African American.

The most common adverse reactions (≥ 20%) were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), and constipation (20%).

Serious adverse reactions were reported in 65% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, pneumonia, sepsis, neutropenia, device-related infection, tremor, encephalopathy, infection, overdose, confusion, *Staphylococcal* bacteremia, and headache.

Adverse reactions of Grade 3 or higher were reported in 80% of patients. Discontinuation of therapy due to adverse reactions occurred in 18% of patients treated with BLINCYTO. The adverse reactions reported most frequently as the reason for discontinuation of treatment included encephalopathy and sepsis. Fatal adverse events occurred in 15% of patients. The majority of these events were infections. No fatal adverse events occurred on treatment among patients in remission.

The adverse reactions with ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher are summarized in Table 2.

Table 2. Adverse Reactions With ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher (N = 212)

Adverse Reaction	Any Grade* (%)	Grade 3 or Higher* (%)
Blood and lymphatic system disorders		
Febrile neutropenia	25	23
Anemia	18	13

Neutropenia	16	15
Thrombocytopenia	11	8
Leukopenia	9	8
Gastrointestinal disorders		
Nausea	25	0
Constipation	20	< 1
Diarrhea[†]	20	1
Abdominal pain	15	2
Vomiting	13	0
General disorders and administration site conditions		
Pyrexia	62	7
Peripheral edema	25	< 1
Fatigue	17	1
Chills	15	0
Chest pain	11	1
Immune system disorders		
Cytokine release syndrome	11	1
Infections and infestations		
Other pathogen infections	44	25
Bacterial infections	19	12
Fungal infections	15	7
Viral infections	13	4
Pneumonia	9	8
Sepsis	7	6
Investigations		
Increased alanine aminotransferase	12	6
Increased aspartate aminotransferase	11	4
Increased weight	11	0
Metabolism and nutrition disorders		
Hypokalemia		
Hypomagnesemia	23	6
Hyperglycemia	12	0
Decreased appetite	11	7
Hypophosphatemia	10	3
	6	5
Musculoskeletal and connective tissue disorders		
Back pain	14	2
Pain in extremity	12	1
Bone pain	11	3
Arthralgia	10	2
Nervous system disorders		
Headache	36	3
Tremor[‡]	20	1
Dizziness	14	< 1
Psychiatric disorders		
Insomnia	15	0
Respiratory, thoracic, and mediastinal disorders		
Cough	19	0
Dyspnea[§]	15	5
Skin and subcutaneous tissue disorders		
Rash[¶]	21	2
Vascular disorders		
Hypotension	11	2
Hypertension	8	5

* Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

† Diarrhea includes the following terms: colitis, diarrhea, enteritis, and neutropenic colitis.

‡ Tremor includes the following terms: resting tremor and tremor.

§ Dyspnea includes the following terms: acute respiratory failure, bronchial hyperactivity, bronchospasm, dyspnea, dyspnea exertional, respiratory distress, respiratory failure, and wheezing.

¶ Rash includes the following terms: erythema, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and vesicular rash.

Additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 2 were:

Blood and lymphatic system disorders: leukocytosis (2%), lymphopenia (1%)

Cardiac disorders: tachycardia (8%)

General disorders and administration site conditions: edema (5%)

Immune system disorders: cytokine storm (1%)

Investigations: decreased immunoglobulins (9%), increased blood bilirubin (8%), increased gamma-glutamyl-transferase (6%), increased liver enzymes (1%)

Metabolism and nutrition disorders: tumor lysis syndrome (4%), hypoalbuminemia (4%)

Nervous system disorders: encephalopathy (5%), paresthesia (5%), aphasia (4%), convulsion (2%), memory impairment (2%), cognitive disorder (1%), speech disorder (< 1%)

Psychiatric disorders: confusion (7%), disorientation (3%)

Vascular disorders: capillary leak syndrome (< 1%).

Hypersensitivity reactions related to BLINCYTO treatment were hypersensitivity (1%) and bronchospasm (< 1%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO has been evaluated using either an electrochemiluminescence detection technology (ECL) or an enzyme-linked immunosorbent assay (ELISA) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

In clinical studies, less than 1% of patients treated with BLINCYTO tested positive for binding anti-blinatumomab antibodies. All patients who tested positive for binding antibodies also tested positive for neutralizing anti-blinatumomab antibodies.

Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO. No association was seen between antibody development and development of adverse events.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.

7. DRUG INTERACTIONS

No formal drug interaction studies have been conducted with BLINCYTO. Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine). Adjust the dose of the concomitant drug as needed *[see Clinical Pharmacology (12.2 and 12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies of BLINCYTO in pregnant women. Based on its mechanism of action, BLINCYTO may cause fetal toxicity including B-cell lymphocytopenia when administered to a pregnant woman. BLINCYTO should be used during pregnancy only if the potential

benefit justifies the potential risk to the fetus.

Animal Data
Animal reproduction studies have not been conducted with blinatumomab. In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause embryo-fetal toxicity or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.

8.3 Lactation

It is not known whether blinatumomab is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from blinatumomab, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

There is limited experience in pediatric patients. BLINCYTO was evaluated in a dose-escalation study of 41 pediatric patients with relapsed or refractory B-precursor ALL. The median age was 6 years (range: 2 to 17 years). BLINCYTO was administered at doses of 5 to 30 mcg/m^2/day. The recommended phase 2 regimen was 5 mcg/m^2/day on Days 1-7 and 15 mcg/m^2/day on Days 8-28 for cycle 1, and 15 mcg/m^2/day on Days 1-28 for subsequent cycles. At a higher dose, a fatal cardiac failure event occurred in the setting of life-threatening cytokine release syndrome (CRS) *[see Warnings and Precautions (5.1)]*.

The steady-state concentrations of blinatumomab were comparable in adult and pediatric patients at the equivalent dose levels based on body surface area (BSA)-based regimens.

8.5 Geriatric Use

Of the total number of patients with relapsed or refractory ALL, approximately 13% were 65 years of age and over. Generally, safety and efficacy were similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with BLINCYTO. Elderly patients experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, confusion, and serious infections *[see Warnings and Precautions (5.2) and (5.3)]*.

8.6 Hepatic Impairment

No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with hepatic impairment.

8.7 Renal Impairment

No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with renal impairment. No dose adjustment is needed for patients with baseline creatinine clearance (CrCL) equal to or greater than 30 mL/min. There is no information available in patients with CrCL less than 30 mL/min or patients on hemodialysis *[see Clinical Pharmacology (12.3)]*.

10. OVERDOSAGE

Overdoses have been observed, including one patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care *[see Warnings and Precautions (5.9)]*. Consider reinitiation of BLINCYTO at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion *[see Dosage and Administration (2.1)]*.

11. DESCRIPTION

BLINCYTO (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). BLINCYTO is produced in Chinese hamster ovary cells. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each BLINCYTO package contains 1 vial BLINCYTO and 1 vial IV Solution Stabilizer.

BLINCYTO is supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-use vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5

mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-use vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-use vial of IV Solution Stabilizer contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

12.2 Pharmacodynamics

During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, reduction in peripheral B cells, and transient cytokine elevation.

Peripheral T cell redistribution (ie, T cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of BLINCYTO infusion or dose escalation. T cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in majority patients. Increase of T cell counts above baseline (T cell expansion) was observed in few patients.

Peripheral B cell counts decreased to less than or equal to 10 cells/microliter during the first treatment cycle at doses ≥ 5 mcg/m^2/day or ≥ 9 mcg/day in the majority of patients. No recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 mcg/m^2/day and 1.5 mcg/m^2/day and in a few patients at higher doses.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ were measured, and IL-6, IL-10, and IFN-γ were elevated. The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

12.3 Pharmacokinetics

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/day (approximately equivalent to 9 to 162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady-state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/refractory ALL, the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

Distribution
The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with continuous intravenous infusion of blinatumomab.

Metabolism
The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, BLINCYTO is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination
The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

Body Weight, Body Surface Area, Gender, and Age
Results of population pharmacokinetic analyses indicate that age (18 to 80 years of age), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57 m^2) do not influence the pharmacokinetics of blinatumomab.

Renal Impairment
No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment.

Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal impairment (CrCL ranging from 30 to 59 mL/min, N = 21)

and normal renal function (CrCL more than 90 mL/min, N = 215). However, high interpatient variability was discerned (CV% up to 95.6%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function. There is no information available in patients with severe renal impairment (CrCL less than 30 mL/min) or patients on hemodialysis.

Drug Interactions
Transient elevation of cytokines may suppress CYP450 enzyme activities *[see Drug Interactions (7) and Clinical Pharmacology (12.2)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.

No studies have been conducted to evaluate the effects of blinatumomab on fertility. A murine surrogate molecule had no adverse effects on male and female reproductive organs in a 13-week repeat-dose toxicity study in mice.

14. CLINICAL STUDIES

14.1 Acute Lymphoblastic Leukemia

The safety and efficacy of BLINCYTO were evaluated in an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic hematopoietic stem cell transplantation [HSCT], and had ≥ 10% blasts in bone marrow).

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. The treated population included 185 patients who received at least 1 infusion of BLINCYTO; the median number of treatment cycles was 2 (range: 1 to 5). Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO. Among treated patients, the median age was 39 years (range: 18 to 79 years), 63 out of 185 (34.1%) had undergone HSCT prior to receiving BLINCYTO, and 32 out of 185 (17.3%) had received more than 2 prior salvage therapies.

The primary endpoint was the complete remission/complete remission with partial hematological recovery (CR/CRh*) rate within 2 cycles of treatment with BLINCYTO. Seventy-seven out of 185 (41.6%) evaluable patients achieved CR/CRh* within the first 2 treatment cycles, with the majority of responses (81%, 62 out of 77) occurring within cycle 1 of treatment. See Table 3 for efficacy results from this study. The HSCT rate among those who achieved CR/CRh* was 39% (30 out of 77).

Table 3. Efficacy Results in Patients ≥ 18 Years of Age With Philadelphia Chromosome-Negative Relapsed or Refractory B-cell precursor Acute Lymphoblastic Leukemia (ALL)

	N = 185		
	CR*	**CRh*†**	**CR/CRh***
n (%) [95% CI]	60 (32.4) [25.7–39.7]	17 (9.2) [5.4–14.3]	77 (41.6) [34.4–49.1]
MRD response‡			
n1/n2 (%)§ [95% CI]	48/60 (80.0) [67.7–89.2]	10/17 (58.8) [32.9–81.6]	58/77 (75.3) [64.2–84.4]
DOR/RFS¶			
Median (months) (range)	6.7 (0.46–16.5)	5.0 (0.13–8.8)	5.9 (0.13–16.5)

* CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

† CRh* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

‡ MRD (minimal residual disease) response was defined as MRD by PCR < 1 x 10^{-4}

§ n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponders.

¶ DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* to relapse or death, whichever is earlier.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each BLINCYTO package (NDC 55513-160-01) contains:

- One BLINCYTO 35 mcg single-use vial containing a sterile, preservative-free, white to off-white lyophilized powder and
- One IV Solution Stabilizer 10 mL single-use glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution. **Do not use the IV Solution Stabilizer to reconstitute BLINCYTO.**

16.2 Storage and Handling

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze.

17. PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide.

Advise patients to contact a healthcare professional for any of the following:

- Signs and symptoms that may be associated with cytokine release syndrome and infusion reactions including pyrexia, fatigue, nausea, vomiting, chills, hypotension, rash, and wheezing *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Signs and symptoms of neurological toxicities including convulsions, speech disorders, and confusion *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Signs and symptoms of infections including pneumonia *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*

Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. Patients should be advised that they may experience neurological events *[see Warnings and Precautions (5.6)]*.

Inform patients that:

- It is very important to keep the area around the intravenous catheter clean to reduce the risk of infection.
- They should not adjust the setting on the infusion pump. Any changes to pump function may result in dosing errors. If there is a problem with the infusion pump or the pump alarms, patients should contact their doctor or nurse immediately.

[Amgen Logo]

BLINCYTO (blinatumomab)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License No. 1080

Patent: http://pat.amgen.com/blincyto/

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Medication Guide

BLINCYTO™ (blin sye' toe)
(blinatumomab)
for injection

Read this Medication Guide before you receive BLINCYTO and before each BLINCYTO infusion. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about BLINCYTO?

Call your healthcare provider or get emergency medical help right away if you get any of the symptoms listed below.

BLINCYTO may cause serious side effects that can be severe, life-threatening, or lead to death, including:

- **Cytokine Release Syndrome (CRS) and Infusion Reactions. Symptoms of CRS and infusion reactions may include:**
  - fever
  - tiredness or weakness
  - dizziness
  - headache
  - low blood pressure
  - nausea
  - vomiting
  - chills
  - face swelling
  - wheezing or trouble breathing
  - skin rash

- **Neurologic problems. Symptoms of neurologic problems may include:**
  - seizures
  - difficulty in speaking or slurred speech
  - loss of consciousness
  - confusion and disorientation
  - loss of balance

Your healthcare provider will check you for these problems during treatment with BLINCYTO. Your healthcare provider may temporarily stop or completely stop your treatment with BLINCYTO, if you have severe side effects.

See **"What are the possible side effects of BLINCYTO?"** below for other side effects of BLINCYTO.

What is BLINCYTO?

BLINCYTO is a prescription medicine used to treat a certain type of acute lymphoblastic leukemia (ALL). Acute lymphoblastic leukemia is a cancer of the blood in which a particular kind of white blood cell is growing out of control.

There is limited experience in using BLINCYTO in children.

Who should not receive BLINCYTO?

Do not receive BLINCYTO if you are allergic to blinatumomab or to any of the ingredients of BLINCYTO. See the end of this Medication Guide for a complete list of ingredients in BLINCYTO.

What should I tell my healthcare provider before receiving BLINCYTO?

Before you receive BLINCYTO, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of neurological problems, such as seizures, confusion, trouble speaking or loss of balance.
- have an infection.
- have ever had an infusion reaction after receiving BLINCYTO or other medications.
- are pregnant or plan to become pregnant. BLINCYTO may harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with BLINCYTO.
- are breastfeeding or plan to breastfeed. It is not known if BLINCYTO passes into your breast milk. You and your healthcare provider should decide if you will take BLINCYTO or breastfeed.You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider when you get a new medicine.

How will I receive BLINCYTO?

- BLINCYTO will be given to you by intravenous (IV) infusion into your vein by an infusion pump.
- You will receive BLINCYTO by continuous IV infusion for 4 weeks (28 days), followed by a 2 week break during which you will not be given BLINCYTO. This is one treatment cycle. After the 2 week break, your healthcare provider will decide if you will be given additional treatment cycles of BLINCYTO.
- Your healthcare provider may give you BLINCYTO in a hospital or clinic for the first 9 days of the first treatment cycle and for the first 2 days of the second cycle to check you for side effects. If you receive additional treatment cycles of BLINCYTO or if your treatment is stopped for a period of time and restarted, you may also be treated in a hospital or clinic.

- Your healthcare provider may change your dose of BLINCYTO, delay, or completely stop treatment with BLINCYTO if you have certain side effects.
- Your healthcare provider will do blood tests during treatment with BLINCYTO to check you for side effects.
- Before you receive BLINCYTO, you will be given a corticosteroid medicine to help reduce infusion reactions.
- It is very important to keep the area around the IV catheter clean to reduce the risk of getting an infection.Your healthcare provider will show you how to care for your catheter site.
- **Do not change the settings on your infusion pump**, even if there is a problem with your pump or your pump alarm sounds. Any changes to your infusion pump settings may cause a dose that is too high or too low to be given.

Call your healthcare provider or nurse right away if you have any problems with your pump or your pump alarm sounds.

What should I avoid while receiving BLINCYTO?

Do not drive, operate heavy machinery, or do other dangerous activities while you are receiving BLINCYTO because BLINCYTO can cause neurological symptoms such as dizziness, seizures, and confusion.

What are the possible side effects of BLINCYTO?

See "What is the most important information I should know?"

BLINCYTO may cause serious side effects, including:
- **Infections.** BLINCYTO may cause life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop an infection.
- **Low white blood cell counts (neutropenia).** Neutropenia is common with BLINCYTO treatment and may sometimes be life-threatening. Low white blood cell counts can increase your risk of infection. Tell your healthcare provider right away if you get a fever.
- **Abnormal liver blood test.** Your healthcare provider will do blood tests before you start BLINCYTO and during treatment with BLINCYTO to check your liver.

The most common side effects of BLINCYTO include:
- fever
- headache
- swelling of hands, ankles or feet
- nausea
- constipation
- shaking (tremor)
- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side of effects of BLINCYTO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BLINCYTO?

Intravenous bags containing BLINCYTO for infusion will arrive in a special package.
- Do not open the package.
- Do not freeze the package.
- The package containing BLINCYTO will be opened by your healthcare provider and stored in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 8 days.
- Do not throw away (dispose of) any BLINCYTO in your household trash. Talk with your healthcare provider about disposal of BLINCYTO and used supplies.

Keep BLINCYTO and all medicines out of reach of children.

General information about BLINCYTO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BLINCYTO for a condition for which it was not prescribed. Do not give BLINCYTO to other people even if they have the same symptoms that you have. It may harm them.

If you would like more information about BLINCYTO, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about BLINCYTO that is written for health professionals.

For more information, go to www.blincyto.com or call Amgen at 1-800-772-6436.

What are the ingredients in BLINCYTO?

Active ingredient: blinatumomab
Inactive ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, trehalose dehydrate, sodium hydroxide and water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

[Amgen Logo]

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Issued: 12/2014

1xxxxxx – v1

1 BLINCYTO™ Single Use Vial

1 IV Solution Stabilizer Vial

NDC 55513-160-01

AMGEN®

BLINCYTO™

(blinatumomab)

for Injection

35 mcg/vial

35 mcg/vial

For Intravenous Infusion Only

Store at 2°C to 8°C (36°F to 46°F).

Store in carton to protect from light.

DO NOT SHAKE reconstituted solution.

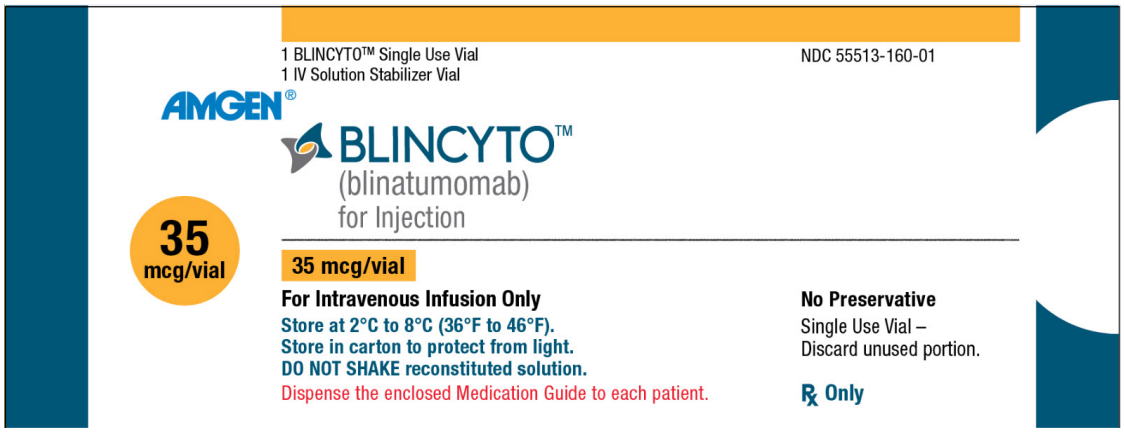
Dispense the enclosed Medication Guide to each patient.

No Preservative

Single Use Vial –

Discard unused portion.

Rx Only



BLINCYTO
blinatumomab kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55513-160

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-160-01	1 in 1 PACKAGE; Type 0: Not a Combination Product		

Quantity of Parts		
Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	3.088 mL
Part 2	1 VIAL	10.6 mL

Part 1 of 2

BLINCYTO

blinatumomab injection, powder, lyophilized, for solution

Product Information			
Item Code (Source)	NDC:55513-150		
Route of Administration	INTRAVENOUS	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
BLINATUMOMAB (UNII: 4FR53SIF3A) (BLINATUMOMAB - UNII:4FR53SIF3A)	BLINATUMOMAB	12.5 ug in 1 mL

Inactive Ingredients	
Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	1.19 mg in 1 mL
LYSINE HYDROCHLORIDE (UNII: JNJ23Q2COM)	8.27 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.23 mg in 1 mL
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	34 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-150-01	3.088 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125557	12/18/2014	

Part 2 of 2

IV STABILIZER

iv stabilizer solution

Product Information			
Item Code (Source)	NDC:55513-155		
Route of Administration	INTRAVENOUS	DEA Schedule	

Inactive Ingredients	
Ingredient Name	Strength
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	5.25 mg in 1 mL
LYSINE HYDROCHLORIDE (UNII: JNJ23Q2COM)	228.38 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	10 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-155-01	10.6 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125557	12/18/2014	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125557	12/18/2014	

Labeler - Amgen Inc (039976196)

Revised: 12/2014 Amgen Inc